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10/079,241	02/20/2002	Holly Hogrefe	10070543-01	7186
27495	7590	07/18/2008	EXAMINER	
AGILENT TECHNOLOGIES INC			HUTSON, RICHARD G	
P.O BOX 7599				
BLDG E , LEGAL			ART UNIT	PAPER NUMBER
LOVELAND, CO 80537-0599			1652	
			NOTIFICATION DATE	DELIVERY MODE
			07/18/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)
	10/079,241	HOGREFE ET AL.
	Examiner	Art Unit
	Richard G. Hutson	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 11 April 2008.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 64,65,70-82 and 85-97 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 64,65,70-82 and 85-97 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 1/11/2008;5/9/2008.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
- 5) Notice of Informal Patent Application
- 6) Other: _____.

DETAILED ACTION

Applicant's amendment of claims 64, 65, 70-74, 80-82, 85, 86, 88, 89, 91 and 93 94, in the paper of 4/11/2008 is acknowledged. Claims 64, 65, 70-82, 85-97 are at issue and are present for examination.

Applicants' arguments filed on 4/11/2008, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64, 65, 70-82 and 85-97 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 64, 65, 70-82 and 85-97 continue to be found indefinite in that they refer to an amino acid corresponding to Y410, T542, D543, K593, Y595, Y385, G387 and G388 of Pfu DNA polymerase and it is unclear what such an amino acid corresponding to is. This rejection was stated in the previous office action. In response to this rejection applicants have amended the claims to refer to the "wildtype Pfu DNA

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polymerase identified at Accession No. P80061..." and traverse the rejection as it applies to the newly amended claims.

Applicants traverse this rejection on the following basis: Applicants submit that given the state of the art and the conserved nature of the domains recited in the claims, one of skill in the art would readily understand which amino acids in the second DNA polymerase correspond to the recited Pfu DNA polymerase residues.

Applicants submit that the claims recite that the second DNA polymerase comprises: the partitioning domain sequence YXGG (SEQ ID NO:6)¹ or SYTGGF (SEQ ID NO:7)2; the polymerase domain sequence DXXSLYP (SEQ ID NO: 1); the polymerase domain sequence YIDTDG (SEQ ID NO:21); and the polymerase domain sequence KXY. Applicants submit as disclosed in the specification and known in the art, these partitioning and polymerase domain sequences are common to a number of Archaeal DNA polymerases, including Pfu, Tgo, KOD, Tli, and Deep Vent .

Applicants submit that the amino acid sequence of the wild type Pyrococcus furiosis (Pfu) DNA polymerase was known and published under Accession Number P80061 and Genbank Accession Number U84155 and the residues recited in the claims (Y410, T542, D543, K593, Y595, Y385, G387, and G388) represent amino acid residues in the known, wild type Pfu amino acid sequence, with each residue falling into one of the conserved polymerase or partitioning domains recited in the claims.

As to the Office's second point regarding the specific amino acid sequence of the Pfu DNA polymerase, Applicants submit that because the amino acid sequence of the

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Pfu DNA polymerase was known as of the filing date of the instant application, the metes and bounds of the claims are clear.

Applicants submit that 35 U.S.C. 112, second paragraph, does not require the recitation of a specific amino acid sequence to delineate the metes and bounds of claimed subject matter when the amino acid sequence was known in the art. As one of skill in the art would have in mind the actual amino acid sequence of the known Pfu DNA polymerase, there is nothing unclear about the scope of the claims.

Nevertheless, while not acquiescing to the rejection, Applicants have amended the claims to recite the "wild type" Pfu DNA polymerase "identified at Accession No. P80061 ." Applicants submit that support for this amendment is found throughout the specification, including, for example, at page 26 and that this amendment makes explicit what was already implicit in the claim and does not change the claim's scope. Applicants respectfully request that the Office withdraw this rejection.

Applicant's amendment and complete argument is acknowledged and has been carefully considered, however, is not found persuasive for the reasons previously made of record and repeated herein.

While the state of the art and the conserved nature of the domains recited in the claims, are appreciated this does not clarify the points raised in the rejection with regard to the indefiniteness of referring to an amino acid position corresponding to an amino acid position absent a reference amino acid sequence. While applicants note each of the domains that exist in the claimed or referenced DNA polymerases, and further note

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that many of the referred to amino acid positions exist within these domains, this is not a limitation of the claims and thus the specific position referred to by applicants remains indefinite.

Applicants submission that the amino acid sequence of the wild type Pyrococcus furiosis (Pfu) DNA polymerase was known and published under Accession Number P80061 and Genbank Accession Number U84155 and the residues recited in the claims (Y410, T542, D543, K593, Y595, Y385, G387, and G388) represent amino acid residues in the known, wild type Pfu amino acid sequence is appreciated, however, it remains that applicants reference of “the wildtype Pfu DNA polymerase” is indefinite in that the sequence of a Genbank Accession number is not definite as these are subject to change. The reference to a Genbank Accession number in the claims is an attempt to incorporate essential subject matter by reference, which is improper. Such a reference to a Genbank Accession number without the corresponding sequence identifier (SEQID NO:) continues to render the claims indefinite.

Claims 64, 65, 70-82 and 85-97 continue to be found further indefinite in that they each recite “reduced 5’-3’ DNA polymerization activity” which is relative terminology and it is unclear what the reduced 5’-3’ DNA polymerization activity is relative to.

This rejection was stated in the previous office action as it applied to the previous claims.

Applicants submit that they have amended claims 64, 85, and 86 to recite that the second enzyme possesses reduced 5' - 3' polymerization activity as compared to

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the wild type form of the second enzyme, making explicit what was already implicit in the claims.

Applicant's amendment and complete argument is acknowledged and has been carefully considered, however, is not found persuasive for the reasons previously made of record and repeated herein. It remains that as discussed above, the wildtype form of the second enzyme is unclear, as there may exist a number of different "wildtype forms" of the enzyme. It is suggested that reference to a specific amino acid sequence of the wildtype form may be helpful in overcoming this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64, 65, 70-82 and 85-97 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 64, 65, 70-82 and 85-97. In response to this rejection applicants have amended claims 64, 65, 70-74, 80-82, 85, 86, 88, 89, 91 and 93 9 and traverse the rejection as it applies to the newly amended claims.

Applicants continue to traverse the rejection on the following basis. Applicants continue to submit that the Office must set forth express findings that support the lack of written description conclusion. Specifically the findings should: identify the claim limitations at issue and establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure. Applicants submit that the Office has not set forth findings of such.

In supporting applicant's position, applicants submit applicants interpretation of the guidelines and applicants further submit that that they have amended the claims such that they now recite a number of domain sequences that must be present in the claimed polymerases. Applicants also note how the skilled artisan recognizes that these domains are found throughout the Archaeal DNA polymerases. Applicants further note that the second DNA polymerase must comprise an amino acid substitution (See above rejection under 112 second paragraph) and certain functional activities.

Applicant's amendment and complete argument is acknowledged and has been carefully considered, however, is not found persuasive on the following basis.

With respect to the identification of the claim limitations at issue, applicants attention continues to drawn to applicants claims which are drawn to an enzyme mixture comprising a first enzyme comprising any DNA polymerase or reverse transcriptase and a second enzyme comprising any DNA polymerase comprising four domains and comprising a mutation such that the recited mutant DNA polymerase has limited if any structural limitations and only functional limitations (See also above rejection under 112

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second paragraph). It is this basis that establishes a *prima facie* case of lack of written description because applicants continue to claim a second DNA polymerase which has a specific functional feature without an associated structural feature. While applicants continue to cite that the claimed enzymes require certain domains, the recited polymerases are not required to comprise these domains by virtue that they encompass those which are mutated, thus eliminating any domain structure.

These are thus the reasons why a person skilled in the art at the time the application would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure.

As amended applicants claims continue to be drawn to an enzyme mixture comprising a first and a second enzyme, wherein said first enzyme is any enzyme which comprises any 5'-3' polymerization activity and said second enzyme is a mutant DNA polymerase comprising a mutation selected from the group consisting of Y410, T542, D543, K593, Y595, Y385, G387 and G388.

While applicants amendment of the recited mutant DNA polymerase to require certain structural domains is helpful in overcoming the rejection, it remains that applicants have not adequately described the referred to mutant DNA polymerases. Specifically with respect to the structure to function description of these mutants.

Given this lack of additional representative species of those enzymes having reduced 5'-3' polymerization activity as compared to the wildtype (See above rejection under 112 second paragraph), as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms

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that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 64, 65, 70-82 and 85-97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme mixture comprising a DNA polymerase and a Reverse Transcriptase and a *Pfu* DNA polymerase which comprises the amino acid sequence of SEQ ID NO: 19 with a mutation selected from the group consisting of Y410, T542, D543, K593, Y595, Y385, G387 and G388, does not reasonably provide enablement for any enzyme mixture comprising first enzyme comprising a 5'-3' polymerization activity and a DNA polymerase comprising one or more mutations at positions Y410, T542, D543, K593, Y595, Y385, G387 and G388 of the wildtype *Pfu* DNA polymerase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 4, 65, 70-82 and 85-97. In response to this rejection applicants have amended claims 64, 65, 70-74, 80-82, 85, 86, 88, 89, 91 and 93 9 and traverse the rejection as it applies to the newly amended claims.

Applicant's amendment of the claims with respect to the first enzyme is appreciated. Applicants continue to traverse the rejection on the following basis. Applicants submit that with respect to the second enzyme, Applicants continue to submit that the claims recite that the second enzyme is a DNA polymerase comprising the partitioning domain sequence YXGG, the polymerase domain sequence DXXSLYP, the polymerase domain sequence YIDTDG, and the polymerase domain sequence KXY, and that the second enzyme has reduced 5' - 3' DNA polymerization activity and that the specification teaches that these partitioning and polymerase domain sequences are common to a number of Archaeal DNA polymerases, including Pfu, Tgo, KOD, Tli, and Deep Vent (see page 27-29). Applicants submit that thus, the amended claims now place clear structural limitations on the claimed second enzyme, regardless of what mutations other than those specifically recited, may be encompassed by the use of the phrase "comprising an amino acid substitution". As discussed above while applicants continue to cite the claimed structural limitation of the claims, these are not found to be such given that applicants claims allow these structural limitations to be mutated.

Applicants presentation of references in the art which shows the skill and knowledge in the art is appreciated, however, it remains that there is an insufficient correlation between applicants recited functional mutants and the claimed structural limitations.

Applicant's argument continues to be acknowledged and has been carefully considered, however, is not found persuasive for the reasons previously made of record and repeated herein.

Applicants traversal with respect to the second enzyme of the claimed mixture, that applicants have amended the claims to require that the second enzyme is a DNA polymerase comprising the partitioning domain sequence YXGG, the polymerase domain sequence DXXSLYP, the polymerase domain sequence YIDTDG, and the polymerase domain sequence KXY, and that the second enzyme has reduced 5' - 3' DNA polymerization activity and that the specification teaches that these partitioning and polymerase domain sequences are common to a number of Archaeal DNA polymerases, including Pfu, Tgo, KOD, Tli, and Deep Vent is also acknowledged. While this amendment is helpful in identifying those encompassed mutant DNA polymerases, the recited structural domains required by the mutant DNA polymerases remain insufficient to enable the full scope of those DNA polymerase mutants encompassed by the claims, by virtue that the encompassed mutations negate the cited domain sequences.

It continues that applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any enzyme mixture comprising any mutant DNA polymerase with the specified function, motifs and specified mutations. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those mutant polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in

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the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 64, 65, 70-82, 85-97 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6, 9-14, 18, 20-22 and 36-51 of copending Application No. 10/035,091. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed enzyme mixtures of the instant application, comprising a first enzyme and a second enzyme wherein said first enzyme comprises a Archaeal DNA polymerase and said second enzyme is a mutant Archaeal DNA polymerase comprising a 3'-5' exonuclease activity and a reduced polymerization activity and having a mutation at an amino acid position selected from the group consisting of D405, Y410, T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon

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are anticipated by and thus obvious over the corresponding claims of copending Application No. 10/035,091, drawn to a enzyme mixture comprising a first enzyme and a second enzyme wherein said first enzyme comprises a DNA polymerization activity and said second enzyme is a mutant Pfu DNA polymerase having a mutation at an amino acid position selected from the group consisting of D405, Y410, T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant continued acknowledgment of this provisional rejection is acknowledged, as well as applicant's continued statement of their intent of filing a terminal disclaimer as a means of overcoming the rejection at the time at which the claims are found otherwise allowable.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
7/2/2008

/Richard G Hutson, Ph.D./
Primary Examiner, Art Unit 1652